222 Human Coronaviruses

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Coronaviridae are enveloped nonsegmented, single-stranded, positive-sense RNA viruses named after their corona- or crown-like surface projections seen on electron microscopy that correspond to large surface spike proteins (Figures 222-1 and 222-2). Coronaviruses are host-specific and can infect humans as well as a variety of different animals, causing diverse clinical syndromes.[1] Three serologically and genetically distinct groups of coronaviruses have been described. Human coronaviruses (HCoVs) are part of groups 1 and 2 and primarily cause a variety of respiratory tract infections[1] (Table 222-1).

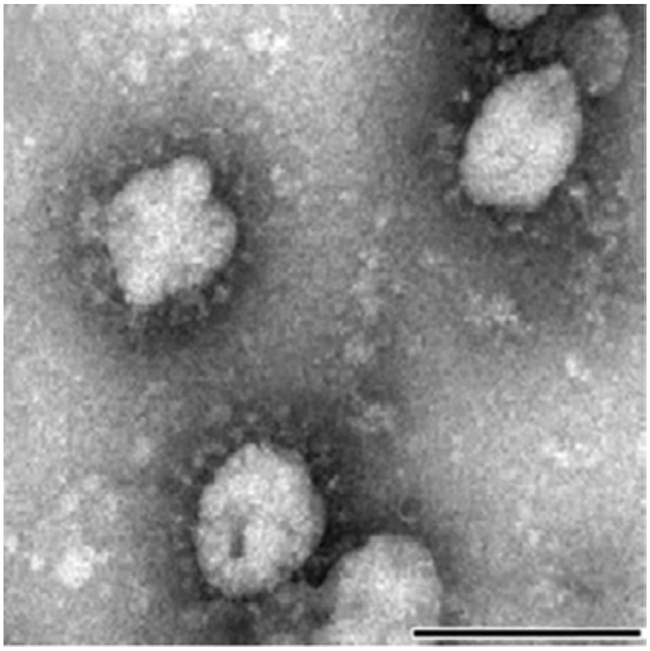

Figure 222-1. Electron micrograph of a typical coronavirus. Negative-contrast electron micrograph of severe acute respiratory syndrome coronaviruses (SARS-CoV). The typical crown-like spike proteins on the surface of the coronavirus particles are shown. Bar = 100 nm. (From Kuiken T, Fouchier RA, Schutten M, et al. Newly discovered coronavirus as the primary cause of severe acute respiratory syndrome. Lancet 2003;362:263–270.)

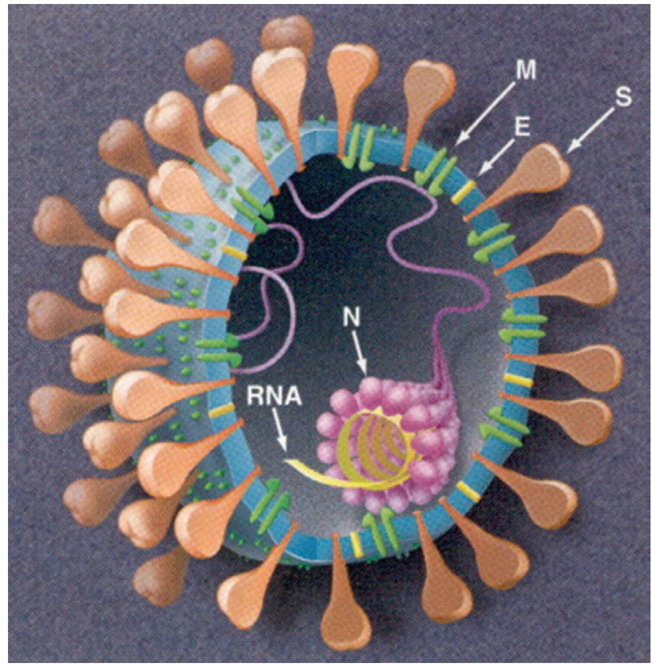

Figure 222-2. Pictorial illustration of a typical coronavirus. The organization of the spike (S), membrane (M), and envelope (E) glycoproteins is shown. The RNA is protected by the nucleocapsid proteins (N). (From Holmes KV, Enjuanes L. The SARS coronavirus: a postgenomic era. Science 2003;300:1377–1378.)

TABLE 222-1. Human and Representative Animal Coronaviruses (CoV)

Group	Common Name of Virus	Acronym	Host	Associated Diseases
1	Human CoV-229E	HCoV-229E	Human	Respiratory tract infection
	Human CoV-NL63	HCoV-NL63	Human	Respiratory tract infection
	Feline infectious peritonitis virus	FIPV	Cat	Hepatitis, respiratory tract, enteric, and neurologic infection
2	Human CoV-OC43	HCoV-OC43	Human	Respiratory tract infection
	Human CoV-HKU1	HCoV-HKU1	Human	Respiratory tract infection and possibly gastroenteritis
	Severe acute respiratory syndrome-CoV[a]	SARS-CoV[a]	Human	Severe acute respiratory syndrome (SARS)
	Mouse hepatitis virus	MHV	Mouse	Hepatitis, encephalitis, and enteric infection
3	Infectious bronchitis virus	IBV	Chicken	Respiratory tract and enteric infection

[a]*SARS-CoV appears to be an outlier of group 2 but some phylogenetic analyses suggest it is the first member of a fourth group of coronaviruses.*[131]

EPIDEMIOLOGY

In the 1930s, coronaviruses were recognized as disease agents in animals.[2] Thirty years later, coronaviruses were identified as agents of respiratory tract infections in humans. The first recognized HCoVs included 229E and OC43. Less well recognized strains, such as B814, OC16, OC37, and OC48, also were described but were not investigated further and to date little is known regarding their prevalence and associated clinical illnesses.[3–5] Coronavirus-like particles also have been detected in stool as possible enteric pathogens, primarily in infants with gastroenteritis and necrotizing enterocolitis, but further characterization has been possible because viruses have not been culturable from these specimens.[6–8] Dramatically, in 2003, severe acute respiratory syndrome (SARS)-CoV was identified as a novel respiratory pathogen responsible for a global outbreak of SARS. This outbreak lasted 9 months and ultimately resulted in 8098 people infected and 774 deaths.[9–13] Most experts believe SARS-CoV evolved from a natural reservoir of SARS-CoV-like viruses in horseshoe bats, with civet cats serving as intermediate hosts.[14–18] Finding a novel HCoV initiated a renewed interest in CoV research and 2 years later, NL63 (referred to in various publications as NL and NH) and HKU1 were identified as newly recognized HCoVs.[19–21] HCoV-NL63 has since been shown to have been present in human respiratory samples as early as 1981.[22] How HCoV-NL63 and HCoV-HKU1 relate to HCoVs originally described in the 1960s, such as B814, OC16, OC37, and OC48, or the enteric coronavirus-like particles detected in stool, is unclear.[23]

HCoVs other than SARS-CoV are found worldwide and cause disease predominantly in winter and spring months in temperate climates.[22,24] Seroprevalence data suggest that exposure is common in early childhood.[25] Approximately 90% of adults are seropositive for HCoV-229E, HCoV-OC43, and HCoV-NL63 and 60% for HCoV-HKU1.[26] SARS-CoV, on the other hand, has not been identified since December 2003/January 2004 when 4 sporadic cases of SARS with no associated transmission were identified in China[27], community-acquired and 13 cases of laboratory-acquired SARS (2 isolated cases and a cluster of 11 cases with 1 death) were identified in Southeast Asia related to breaches in biosafety practices in different laboratories cultivating SARS-CoV.[28–30] Modes of transmission for HCoV other than SARS-CoV have not been well studied. However, based on studies of other respiratory viruses, it is likely that transmission occurs primarily via a combination of droplet and direct and indirect contact spread.[31] Which mode is most important remains to be determined, and the possible role of aerosol spread needs further study. Droplet and direct contact spread are likely the most common modes of transmission for SARS-CoV, although evidence for indirect contact spread and aerosol spread also exists.[32–39] There is no evidence of vertical transmission of SARS-CoV.[40,41]

Based on data for HCoV-229E and HCoV-OC43, HCoVs other than SARS-CoV are most likely to be transmitted during the first few days of illness when symptoms and viral load in the respiratory tract is highest.[42,43] Further study is needed to confirm if this also is the case for the more recently identified HCoV-NL63 and HCoV-HKU1. SARS-CoV, on the other hand, is most likely to be transmitted during the second week of illness when both symptoms and viral load in the respiratory tract peak.[44–46]

The incubation period for HCoV-229E is 2 to 5 days (median 3 days).[43,47] Further study is needed to confirm the incubation periods for the other non-SARS-HCoVs. The incubation period for SARS-CoV is 2 to 10 days (median 4 days).[44]

PATHOGENESIS AND IMMUNITY

The pathogenesis of HCoV has been best described for 229E and SARS-CoV. For SARS-CoV, most evidence is from infections in adults given that few children were affected by the 2002–2003 outbreak.[48] More study is needed to further understand the pathogenesis of other HCoVs.

HCoV-229E infections are initiated through inoculation of mucosal surfaces of the respiratory tract. HCoV-229E infection is associated with nasal mucosal plasma exudation and increased levels of interferon-γ (IFN-γ) in nasal lavage specimens, which correlate with symptom severity.[49,50] Viral load in respiratory tract specimens peaks within the first 3 days after infection and drops off dramatically at 1 week, correlating with development and subsequent improvement in symptoms.[42,51] Antibodies can be detected starting at 1 week, correlating with the drop in viral load, and reach a maximum levels approximately 1 week later.[52] Thereafter, antibody titers decline slowly. Immunity is not complete and reinfection is common.[52,53] Higher circulating antibody levels and especially levels of specific IgA anti-HCoV correlate with reduced virus shedding and reduced symptoms upon re-exposure.[52,54]

SARS-CoV infection most likely is initiated through inoculation of the respiratory tract mucosa. Subsequent viremia is followed by predominant replication in the lung and gastrointestinal tract.[55,56] Replication at other sites also likely occurs given the wide distribution of SARS-CoV in tissues examined at autopsy.[57,58] Peak viral loads in nasopharyngeal specimens are noted during the second week of symptoms.[45,56] A rise in SARS-CoV specific antibodies typically is seen starting at week 2 after infection. Increasing antibody titers and symptomatic improvement during the second and third week are associated with a fall in the quantity of SARS-CoV, as measured by reverse transcriptase polymerase chain reaction (RT-PCR).[45,59] Paradoxically, despite a fall in SARS-CoV viral load and a rise in SARS-specific antibodies, clinical deterioration is observed in some patients. This suggests that host immune responses likely are responsible for clinical deterioration.[45] Indeed, SARS is associated with an elevation of IFN-γ, inflammatory cytokines interleukin (IL)-1, IL-6, and IL-12 as well as elevations in neutrophil chemokine IL-8, monocyte chemoattractant protein 1, and IFN-γ-inducible protein-10. Levels of IL-6 correlate with severity of disease.[60,61]

CLINICAL MANIFESTATIONS

HCoVs 229E, OC43, NL63, and HKU1, are commonly associated with the common cold, typically characterized by rhinorrhea, nasal congestion, sore throat, sneezing, and cough that may be associated with fever.[20,22,51,62–65] Together, they are the next most common cause of the common cold after rhinoviruses.[66,67] Based on data for HCoV-229E, symptoms typically peak on day 3 or 4 of illness and are self-limiting.[51,68] These HCoVs also may be associated with acute otitis media or exacerbations of asthma.[22,63,65,69,70] Less frequently, these viruses are associated with lower respiratory tract infections including bronchiolitis and pneumonia, primarily in infants and immunocompromised children and adults.[21,21,63,65,71–79] Compared with other HCoVs, HCoV-NL63 more frequently is associated with croup, being the next most common isolate after parainfluenza virus type 1.[80,81] A possible association of HCoV-NL63 with Kawasaki disease was not substantiated.[82,83] HCoV-HKU1 has been associated with symptoms of gastroenteritis, including vomiting and diarrhea, that typically occur along with respiratory symptoms.[65,70,84] HCoV-HKU1 also appears to be more frequently associated with febrile seizures compared with other HCoVs.[65,70]

Compared with other HCoVs, SARS-CoV is associated with more severe symptoms.[85–87] SARS-CoV disproportionately affects adults, who typically manifest fever, myalgia, headache, malaise, and chills followed by a nonproductive cough and dyspnea 3 to 5 days later. Approximately 25% develop watery diarrhea. Respiratory distress progresses to require intubation and ventilation in 25% of cases. The overall associated mortality rate is approximately 10%, most deaths occurring in the third week of illness.[86] The case-fatality rate in persons over the age of 60 approaches 50%.[88] Typical laboratory abnormalities include lymphopenia and increased serum lactate dehydrogenase and creatine kinase levels.[89,90] The majority have progressive unilateral or bilateral ill-defined air-space infiltrates on chest imaging.[89,91–93] Pneumothoraces and other signs of barotrauma are common in critically ill patients receiving mechanical ventilation.[86]

Infants and children appear to be protected against SARS-CoV infection, and clinical manifestations in infected children are less severe. Notably no infants or children died due to SARS-CoV infection in the 2002–2003 outbreak.[48,94–97] Infants and children <12 years of age who develop SARS typically manifest fever, cough, and rhinorrhea. Associated lymphopenia is less severe and radiographic changes are milder and generally resolve more quickly than in adolescents and adults. Adolescents who developed SARS had clinical courses more closely resembling that of adults, manifesting fever, myalgia, headache, and chills. Adolescents are more likely to develop dyspnea, hypoxemia, and worsening chest radiographic findings. Laboratory abnormalities are comparable with those in adults.

Women infected with SARS-CoV during pregnancy who survive have an increased risk of spontaneous miscarriage, preterm delivery, and intrauterine growth restriction [40,41,98] Two neonates born to mothers with SARS in the 2002–2003 outbreak developed gastrointestinal complications (jejunal perforation, necrotizing enterocolitis with ileal perforation) shortly after birth but neither had clinical evidence of SARS-CoV infection.[41] It is unclear whether these findings were related to complications of maternal SARS-CoV infection or treatments used during pregnancy, such as ribavirin and corticosteroids.

DIAGNOSIS

In the past, the diagnosis of infections due to HCoVs typically was not attempted in clinical settings outside of outbreak situations or epidemiologic surveys. However, the 2002–2003 SARS outbreak renewed interest in identifying the etiology of respiratory tract infections and some specialized laboratories now offer comprehensive diagnostic testing for respiratory tract specimens primarily based on RT-PCR; some panels include detection of HCoV.[65,99] Antibody tests also are available for SARS-CoV.[100]

Upper and lower respiratory tract specimens are the most appropriate samples for viral detection when testing is available.[42,56,63,65,101] Stool samples frequently are positive in patients with SARS and have been positive in some children with HCoV-HKU1 infection.[56,70,84,101] Serum samples may be positive in patients with SARS-CoV. For HCoV-299E and HCoV-OC43, specimens are most likely to be positive during the first few days of illness;[42] whether this also is true for HCoV-NL63 and HCoV-HKU1 needs further study. For SARS-CoV, serum samples for RT-PCR testing are most likely to be positive in the first week of illness,[55,102] but respiratory and stool specimens may not be positive until the second week of illness when symptoms and viral loads peak.[45,56] Compared with adults, infants and children with SARS-CoV infections are less likely to have positive specimens. This is consistent with the milder symptoms and presumed correspondingly lower viral loads in children.[94,95]

Laboratory guidance for SARS-CoV diagnostic testing is available on the Centers for Disease Control and Prevention website.[103] Given the potential for false-positive results and the associated public health implications, testing for SARS-CoV in the absence of known person-to-person transmission of SARS-CoV only should be done with caution, preferably in consultation with regional public health departments, and when there is a high degree of clinical suspicion with no alternative diagnosis.

TREATMENT

Because of mild symptoms and the self-limited nature of HCoV infections other than SARS-CoV, few treatment studies have been performed. Generally, care is supportive. SARS-CoV infections are more serious. Corticosteroids, type 1 IFN agents, convalescent plasma, ribavirin, and lopinavir/ritonavir all have been used to treat SARS.[89,104–107] For most of these treatments, anecdotal reports suggest benefit, and in vitro assays and animal models are supportive.[89,104–116] Despite some reports of anecdotal clinical improvement with ribavirin, however, in vitro studies do not support likely efficacy.[113,117,118] Since the SARS outbreak, other agents have been tested in vitro and appear promising. These include viral entry and protease inhibiting agents, RNA interfering agents, and glycyrrhizin.[119] However, no definitive conclusions can be drawn regarding efficacy of these treatments. This is noteworthy because controlled studies have not been performed for any of these agents, and there are reports of uneventful recovery for patients given supportive care alone. In the event that SARS-CoV re-emerges, clarification of the effectiveness of these treatments through controlled clinical trials will be needed.

PREVENTION

Meticulous hand and respiratory hygiene is the most useful and easily implemented control measure to curb the spread of all respiratory viruses including HCoVs.[120,121] Other preventive measures have been assessed. Prophylactic intranasal IFN-α has been shown to reduce the duration and severity of 229E infection in research settings but has not been used clinically.[122,123] IFN-α has not been studied for prevention of other HCoVs. A proprietary extract of the roots of North American ginseng (*Panax quinquefolium*) has been shown to reduce the number of colds as well as the severity and duration of cold symptoms in adults when taken daily, presumably due to immune stimulation.[124–127] Efficacy for decrease in colds specifically due to HCoVs has not been studied.

Healthcare personnel should wear a mask when evaluating persons with a cough illness and should use a gown, gloves, mask, and eye protection for the duration of illness when caring for children hospitalized with signs and symptoms of a respiratory tract infection.[128] The same precautions, with the replacement of the mask with a respirator, if available, plus negative-pressure isolation are recommended for patients with SARS-CoV infection for the duration of illness or 10 days after resolution of fever, provided respiratory symptoms are absent or improving.[128] Cleaning and disinfection of environmental surfaces that are frequently touched by infected persons, using standard disinfectants, should decrease the potential for indirect transmission of HCoVs via fomites.[129]

The control of the 2002–2003 SARS outbreak is credited to the rapid identification of cases and early implementation of infection control and public health measures including contact tracing and quarantine. If SARS-CoV re-emerges, all measures should be implemented quickly in an attempt to prevent a recurrent worldwide outbreak.[130,131]

Key Points. Epidemiology, Clinical Manifestations, Diagnosis, and Treatment of Human Coronavirus (HCoV) Infections

EPIDEMIOLOGY

- HCoVs 229E, OC43, NL63, and HKU1 – found worldwide; exposure common in early childhood; in temperate climates, primarily causes infections in winter and spring months
- SARS-CoV – not identified in the world since January 2004 (soon after the 2002–2003 global outbreak of SARS); possibility/probability of a large-scale re-emergence of SARS is unknown
- Most common modes of transmission are through droplet and direct and indirect contact

CLINICAL MANIFESTATIONS

- HCoVs 229E, OC43, NL63, and HKU1 – associated with the common cold, acute otitis media, asthma exacerbations, and less frequently, bronchiolitis and pneumonia; HCoV-NL63 – also associated with croup; HCoV-HKU1 – also associated with vomiting and diarrhea frequently with respiratory tract symptoms; appears to be associated more frequently with febrile seizures compared with other HCoVs
- SARS-CoV – associated with SARS with an attendant mortality rate of 10% which primarily affects adults and adolescents; children <12 years of age who develop SARS typically have less severe manifestations (fever, cough, and rhinorrhea)

DIAGNOSIS

- Upper and lower respiratory tract specimens can be tested by HCoV RT-PCR
- Stool samples frequently are positive in patients with SARS-CoV and have been positive in some children with HCoV-HKU1 infection; antibody tests also are available for SARS-CoV

TREATMENT

- HCoVs 229E, OC43, NL63, and HKU1 – supportive care
- SARS-CoV – no definitive treatment can be recommended because of lack of controlled trials

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